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Easily disintegrabl granules c ntg. pharmaceutical - and low substitution degree hydroxypropyl-cellulose, water-soluble binder and water

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Number of Countries: 001 Number of Patents: 001

Patent Family:

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Priority Applications (No Type Date): JP 7775090 A 19770624

Abstract (Basic): JP 54011226 A

Easily disintegrable granules comprise granulated mixt. of (a)

100 pts. wt. powdered main drug; (2) 2-20 pts. wt. low substitution degree

hydroxypropylcellulose comprising particles of hydroxypropyl gp. substitution (mols) of 0.05 is approx. 1.00 per anhydrous glucose unit

and diameter <105 um for >95% of the particles; (c) 0.1 is approx.

10 pts. wt. water soluble binder and (d) water.

As water soluble binder may be used natural prod. e.g. starch, acacia or gelatine, synthetic prod. as e.g. carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylmethylcellulose, polyvinylpyrrolidone or PVA in an

amt. of 1 is approx. 10 wt. % w.r.t. material powder.

Easily disintegrable granules may be produced using water solvent

without problems of fire or explosion caused by organic solvent.

Title Terms: EASY; DISINTEGRATE; GRANULE; CONTAIN; PHARMACEUTICAL; LOW; SUBSTITUTE; DEGREE; HYDROXYPROPYL; CELLULOSE; WATER; SOLUBLE; BIND; WATER

Derwent Class: A96; B07

International Patent Class (Additional): A61K-009/16

## SPECIFICATION

### 1. Title of the invention

Easily disintegrating granule

### 2. Claims

1. An easily disintegrating granule, which comprises a granulated mixture of (1) 100 parts by weight of a powdery basis raw material, (2) 2 to 20 parts by weight of a slightly substituted hydroxypropylcellulose powder in which a hydroxypropyl group substitution mole number per anhydrous glucose unit is 0.05 to 1.00 and which comprises particles, 95% by weight or more of which have a diameter of 105  $\mu$ m or smaller, (3) 0.1 to 10 parts by weight of a water-soluble binder, and (4) water.

### 3. Detailed description of the invention

The present invention relates to an easily disintegrating granule.

Previously, in many cases, a granule has been prepared by a wet method, in which a solution of a binder is added to a powdery basis or a raw material powder containing a powdery basis, an excipient and the like, which is granulated. This wet method is further classified into extrusion granulation, oscillator granulation, rolling granulation and crushing granulation. Among them, an extrusion granulation method is generally used in which a binder solution is added to a raw material powder and, if necessary, a liquid is further added

to mix, which is extruded through a screen.

As a liquid used for adding the aforementioned solution, organic solvents such as acetone, methyl alcohol, ethyl alcohol and isopropyl alcohol, and water are used. However, these organic solvents are flammable and have a risk of fire and explosion. Also from a viewpoint of a price, exploitation of a method using only water is desired. In this case, when an amount of liquid to be added is small, granulation is not sufficiently performed. On the other hand, when the amount is too large, granules extruded through a screen adhere to each other. Therefore, it is necessary to determine a suitable range of addition in advance. However, depending upon the nature of a raw material powder, a suitable range of addition does not exist in a water solvent, that range is very narrow and a stable granule is not obtained. Upon extrusion granulation of such the raw material powder, a method is adopted in which a suitable organic solvent is used in place of water, or an excipient having the better granulating property, for example, lactose or starch is added at a large amount. However, the former has the defect described above. and latter can improve the granulating property and, on the other hand, has the defects that a rate of a basis ingredient to be contained becomes too low and the productivity is lowered.

On the other hand, it is known that slightly substituted

hydroxypropylcellulose which is a cellulose derivative is added to a solid drug as an excipient or a disintegrating agent (JP-B 46-42792, JT-B 48-38858). However, when this is added to a raw material powder to mix, which is granulated using water as a solvent without using any water-soluble binder, even a raw material having the worse granulating property can improve the granulating property. However, a granule obtained by this method has a very long disintegrating time in the living body, has the insufficient strength and, thus, a practical productivity can not be obtained frequently.

The present invention is to provide an easily disintegrating granule which solves such the problem, and relates to an easily disintegrating granule, which comprises a granulated mixture of (1) 100 parts by weight of a powdery basis raw material, (2) 2 to 20 parts by weight of a slightly substituted hydroxypropylcellulose powder in which a hydroxypropyl group substitution mole number per anhydrous glucose unit is 0.05 to 1.00 and which comprises particles, 95% by weight or more of which have a diameter of 105  $\mu$ m or smaller, (3) 0.1 to 10 parts by weight of a water-soluble binder, and (4) water.

This will be explained. The present inventors found that, upon preparation of a granule by a method such as extrusion granulation and the like, by adding slightly substituted hydroxypropylcellulose to a raw material powder,

even a material to be granulated with difficulty can be easily granulated and, at the same time, by adding a water-soluble binder, the disintegrating property in the living body is remarkably improved, a granule having the excellent strength is obtained and, upon this, addition of only water is sufficient, which resulted in completion of the present invention.

When a water-soluble binder is added, a disintegrating time is generally delayed in the case of a tablet. However, it is an unexpected fact that, in the case of a granule, easily disintegrating property is obtained.

It is necessary that a slightly substituted hydroxypropylcellulose powder used in the present invention has a hydroxypropyl group substitution mole number per anhydrous glucose unit ranging 0.05 to 1.00. When the number is below this range, it is difficult to prepare a granule having the large strength. Conversely, when the number is above this range, the workability of extrusion granulation most generally used can be hardly improved. It is also necessary that the powder is a powder comprising particles, 95% by weight or more of which have a particle diameter of 105  $\mu\text{m}$  or smaller, preferably 75  $\mu\text{m}$  or smaller. When the powder is more coarse, clogging of a screen is caused and, not only a granulation rate is lowered, but also the smoothness of a granule surface is lost, leading to remarkable decrease

in the product value. When an amount to be added is too small, the effects of improving the granulating property and the granule strength can not be expected. When the amount is too large, since the content of a basis ingredient is lowered, such the amount is an amount corresponding to 2 to 20% by weight, preferably 3 to 15% by weight relative to a raw material powder.

Many of medicaments are ionic and, when an additive is ionic, quality change of a medicament by a reaction is cared. In particular, when water is added to mix, this reaction is easily caused. However, since slightly substituted hydroxypropylcellulose is nonionic, there is any such the care at all and, thus, it can be applied to all medicaments.

Slightly substituted hydroxypropylcellulose used in the present invention has been previously known, and can be obtained by the known method, for example, by soaking a pulp into an aqueous sodium hydroxide solution having the concentration of 10 to 50%, squeezing it, reacting this and propylene oxide at 20 to 90°C for 2 to 8 hours, or reacting propylene oxide with a powdery pulp in an organic solvent such as isopropyl alcohol, t-butyl alcohol and hexane after addition of an aqueous sodium hydroxide solution, then neutralizing sodium hydroxide, which is purified, dried and crushed.

Examples of a water-soluble binder include natural

products such as starch, gum arabic and gelatin, and synthetic products such as carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxypropylmethylmethylcellulose, polyvinylpyrrolidon and polyvinyl alcohol. These are used at a proportion of 1 to 10% by weight relative to a raw material powder. This binder is generally used after it is dissolved in water to be added at granulation, in advance. However, a powdery binder may be mixed with a raw material powder and slightly substituted hydroxypropylcellulose in advance and, thereafter, water may be added.

An amount of this water-soluble binder to be used is a range of 0.1 to 10 parts by weight, preferably 0.2 to 5 parts by weight relative to 100 parts by weight of a powdery basis raw material. This is because, when the amount to be used is too small, the disintegrating property which is the purpose of the present invention can not be improved and, when the amount is conversely too large, not only disintegration is delayed, but also the granule of the present invention has the adhering property and granulation becomes difficult.

In the practice of the present invention, previously known excipients such as lactose and sucrose may be used.

A powdery basis raw material used upon obtaining of the granule of the present invention is not particularly limited and includes a variety of raw material powders containing a powdery drug ingredient, or a basis ingredient with an

excipient, a bulking agent, a sweetener and other additive ingredients incorporated.

The granule of the present invention can be easily prepared by using slightly substituted hydroxypropylcellulose powder and a water-soluble binder at a relatively small amount, without use of an organic solvent, and without addition of a large amount of an excipient, even in the case of a raw material powder which has been previously difficult to be granulated with a water solvent. For this reason, there is no risk of burn and explosion due to an organic solvent and, furthermore, a granule having a high content of a basis ingredient can be obtained.

In addition, a this integrating time of a granule becomes remarkably short and, not only a rapid-acting drug can be prepared, but also the strength of a granule can be improved as compared with a method in which only slightly substituted hydroxypropylcellulose is added.

Then, Examples are illustrated. Part and % in respective Examples denote part by weight and % by weight, respectively. A disintegrating time and an abrasive wear were for a granule measured under the following conditions, respectively.

Disintegrating time:

Japanese Pharmacopoeia, 9th edition, general test method 33, disintegration test method (using tap water at 37°C)



Abrasive wear:

10 g of granules which had passed through a sieve having an opening of 840 micron and had not passed through a sieve having an opening of 350 micron were placed into a rotating tablet abrasive wear tester, which was rotated by 200 rotations (10 min.), classified through a 350 micron sieve, and a decrease rate in weight (%) of a granule was measured. Example 1, Comparative Examples 1 to 3

95 parts of finely-divided aspirin, 5 parts of slightly substituted hydroxypropylcellulose having a size distribution shown in the following Table 1 and having a substitution mole number per anhydrous glucose unit of 0.30 and 25 parts of a 5% aqueous starch solution were mixed, which was granulated at a rate shown in the following Table 1 using a rotary-type extrusion granulator (screen diameter 12.5 cm, screen hole diameter 0.6 mm) manufactured by Nihonyakugyokikaisha. Then, the granule was dried with a venting dryer at a temperature of a 60°C, and classified using a sieve having an opening of 0.84 mm (JIS standard net sieve).

A disintegrating time and an abrasive wear for granules which had passed through this sieve were examined, and the results thereof are shown in the following Table 1.

For comparison, the same composition except that slightly substituted hydroxypropylcellulose, 90% of which have a size distribution of 105  $\mu$ m or smaller, was used

(Comparative Example 2), the same composition except that a 5% aqueous starch solution was not used at all (Comparative Example 3) and only finely-divided aspirin (Comparative Example 4) were subjected to granulation and sieving treatment, a disintegrating time and an abrasive wear of granules which had passed through a sieve are examined and the results thereof are also shown in the following Table 1.

When a 5% aqueous starch solution was not used at all, water was added at 30% (per unit weight of a mixed powder), and treatment was performed.

Table 1

		Example 1	Comparative Example 1	Comparative Example 2	Comparative Example 3
Particle size of additive (%)	105 - 149 $\mu$ m	1	10	1	
	74 - 105 $\mu$ m	6	15	6	
	74 $\mu$ m or smaller	93	75	93	
Granulation rate (g/min)		110	30	100	Un-granulatable
Physical properties	Disintegrating time (min.)	1	3	16	
	Abrasive wear (%)	0.97	0.80	1.66	

Examples 2 to 3, Comparative Examples 4 to 5

A particle size of slightly substituting hydroxypropylcellulose having a hydroxypropyl group substitution mole number per anhydrous glucose unit shown in the following Table 2 was adjusted by classifying so that a particle diameter 74  $\mu$ m or smaller is 96%, and a particle

diameter between 74 and 105  $\mu$ m is 4%.

Then, 95 parts of finely-divided phenacetin, 5 parts of slightly substituted hydroxypropylcellulose adjusted above and 2 parts of TO-5 (trademane manufactured by Shinetuskagaku, hydroxypropylmethylcellulose) were mixed in a biaxial kneader for 10 minutes, water was added as shown in the following Table 2, mixed for 20 minutes, which was granulated with the same rotary-type extrusion granulator manufactured by Nihonyakugyokikai as that used in Example 1, then dried and classified.

A disintegrating time and an abrasive wear for granules which had passed through this sieve were examined by the method described above, and the results thereof are shown in the following Table 2.

For comparison, the same composition except that Avicel (tradeneme manufactured by Asahikasei, microcrystalline cellulose) was used in place of slightly substituted hydroxypropylcellulose (Comparative Example 4) and the same composition except that hydroxypropylcellulose having a hydroxypropyl group substitution mole number of 1.53 was used (Comparative Example 5) were subjected to granulation, drying and classifying treatment as described above, a disintegrating time and an abrasive wear of granules which had passed through a sieve were examined, and the results are also shown in Table 2.

Table 2

		Comparative Example 4	Example 2	Example 3	Example 5
Additive		Avicel	Slightly substituted hydroxypropyl- cellulose	Same as left	Hydroxypropyl- cellulose
Hydroxypropyl group substitution mole number		0	0.20	0.71	1.53
Amount of water to be added (%)		2.5	2.6	2.4	Ungranulatable
Granulation rate (g/min)		110	120	120	
Physical properties	Disintegrating time (min.)	300	30	5	
	Abrasive wear (%)	1.9	0.8	1.0	

(Provided that, an amount of water to be added is a value per unit weight of a mixed powder)

#### Example 4, Comparative Example 6

Using slightly substituted hydroxypropylcellulose having a substitution mole number per anhydrous glucose unit of 0.22 which had passed through a 149 micron sieve and at a formulation in Table, a test of preparing a spherical granule was performed. First, phenacetin and slightly substituted hydroxypropylcellulose were mixed with a biaxial kneader for 5 hours, a 7% aqueous solution of HPO-SL (tradename manufactured by Nihonsoda, hydroxypropylcellulose) was added, stirred to mix for 5 hours, which was granulated at a rate shown in the following Table 3 using a biaxial extrusion granulator Pelsodable (EXD-60 type (screen hole diameter 1

mm) manufactured by Fujipowdal. Further, a granule was subjected to sphericalization treatment with Melizer Q-400 type manufactured by Fujipowdal, dried at 60°C, which was examined for a disintegrating time, an abrasive wear and appearance, and the results thereof are shown in Table 3.

The same treatment as that described above was performed using lactose and corn starch without addition of slightly substituted cellulose ether, a granule was examined for a disintegrating time, an abrasive wear and appearance, and the results are also shown in Table 3.

An abrasive wear was measured using granules having a particle diameter of 710 to 1410  $\mu\text{m}$  by rotating an abrasive wear tester, and decrease in weight (%) was obtained at a sieve having an opening of 710 micron.

Table 3

No.		Example 4	Comparative Example 6
Formulation	Phenacetin	90 parts	54 parts
	Slightly substituted hydroxypropylcellulose	10 parts	—
	Lactose	—	36 parts
	Corn starch	—	10 parts
HPC-SL aqueous solution Added amount (%)		24	15
Granulation rate (Kg/hour)		40	52
Physical properties	Disintegrating time (sec)	60	90
	Abrasive wear (%)	0.2	1.1
Appearance of granule		Spherical	Slightly elongated